

AMENDMENTS TO THE SPECIFICATION:

Please add the following *new* paragraph on page 1, between lines 2 and 3:

CROSS-REFERENCE TO RELATED APPLICATIONS

This U.S. National stage application claims priority under 35 U.S.C. §119(a) to Japanese Patent Application No.2003-403350, filed in Japan on December 2, 2003, the entire contents of which are hereby incorporated herein by reference.

Please replace the paragraph beginning at page 2, line 17 with the following rewritten version:

For detecting a chemical present in the environment, there is an assay system utilizing toxicity response of a yeast cell (~~Patent Publications 1 and 2~~ See, for example, WO 03/018792 and Japanese Patent Publication No. 2003-061676).

Please remove the paragraph beginning at page 2, line 22 as follows:

~~Patent Publication 1: WO 03/018792~~

~~Patent Publication 2: JP A No. 2003-061676~~

Please replace the heading at page 2, line 25, with the following rewritten version:

SUMMARY OF THE INVENTION ~~Disclosure of the invention~~

Please replace the paragraph beginning at page 3, line 4 with the following rewritten version:

The present inventors accumulated gene information induced by chemicals as shown in ~~Patent Publications 1 and 2~~ WO 03/018792 and Japanese Patent Publication No. 2003-061676, and have been studied a bioassay method utilizing toxicity response of a yeast cell.

A sensitivity for detecting a chemical by bioassay depends on sensitivity of a cell and an organism using as an index on a chemical. Therefore, in a bioassay method utilizing toxicity response of a yeast cell, it is necessary to utilize a yeast cell having a higher sensitivity in order to construct a system of a higher sensitivity. Then, from about 4800 kinds of gene-disrupted strains which can be grown as a homozygous diploid among gene-disrupted strains of 6000 kinds of genes of yeast, gene-disrupted strains having a chemical sensitivity suitable in an assay system for detecting a chemical were selected.

Please replace the paragraph beginning at page 4, line 2 with the following rewritten version:

That is, the present invention relates to:

(1) A first aspect of the present invention is a method of examining whether a chemical is present in a test specimen or not, comprising culturing a gene-disrupted stain of a microorganism in the presence of the test specimen, and using cell response of the gene-disrupted strain to the chemical as an index, preferably the method in which cell response of the gene-disrupted strain to the chemical is life or death of a cell, and/or a change in the proliferating ability, an aspiration amount, enzyme activity and/or gene expression, further preferably

the method in which the change in gene expression is a change in a RNA amount or a mRNA amount, more preferably

the method in which the change in gene expression is measured by reporter gene assay,

Please replace the paragraph beginning at page 4, line 18 with the following rewritten version:

(2) A second aspect of the present invention is the method according to the (1)first aspect, wherein the microorganism is yeast, preferably
the method in which a gene to be disrupted, according to classification of public database: MITS, is classified into

amino acid metabolism (01.01), nitrogen and sulfur metabolism (01.02), nucleotide metabolism (01.03), phosphate metabolism (01.04), C-compound and carbohydrate metabolism (01.05), lipid, fatty acid and isoprenoid metabolism (01.06), metabolism of vitamins, cofactors and prosthetic groups (01.07) of metabolism (01);

DNA processing (03.01), cell cycle (03.03) of cell cycle and DNA processing (03);

mRNA transcription (04.05), RNA transport (04.07) of transcription (04);

ribosome biosynthesis (05.01), translational control (05.07) of protein synthesis (05);

protein targeting, sorting, translocation (06.04), protein modification (06.07), assembly of protein complex (06.10), proteolysis (06.13) of protein fate (06);

nuclear transport (08.01), vesicular transport (Golgi network etc.) (08.07), vacuolar transport (08.13), cellular import (08.19), cytoskeleton-dependent transport (08.22), other intracellular transport activities (08.99) of intracellular transport and transport mechanism (08);

stress response (11.01), toxicification (11.07) of cell rescue, defense and pathogenicity (11);

ionic homeostasis (13.01), cell sensitivity and response (13.11) of intracellular environmental regulation/interaction (13);

cell growth/morphogenesis (14.01), cell differentiation (14.04) of cell fate (14);

cell wall (30.01), cytoskeleton (30.04), nucleus (30.10), mitochondria (30.16) of cell tissue control (30);

ion transporter (67.04), vitamin/cofactor transporter (67.21), transport mechanism (67.50), other transport promotion (67.99) of transport promotion (67);

unclassified (98); and/or

unclassified protein (99), further preferably

the method in which the gene to be disrupted is involved in the function of the following Table 2, more preferably, the method in which the gene to be disrupted is involved in a vacuole, for example, in the case of yeast, specifically, the following YPR036W, YDR027C, YHR026W, YHR039C-A, YKL080W, YLR447C, YGR105W, YKL119C, YHR060W (wherein YHR039C-A is designated as YHR039C-B in some cases),

Please replace the paragraph beginning at page 8, line 7 with the following rewritten version:

~~(3)~~ A third aspect of the present invention is the method according to the ~~(1)~~first aspect, wherein the microorganism is a microorganism other than yeast, and the gene to be disrupted is a gene corresponding to a gene as defined in the (2),

Please replace the paragraph beginning at page 8, line 13 with the following rewritten version:

~~(4)~~ A fourth aspect of the present invention is a kit comprising a gene-disrupted strain of a microorganism, which is used for examining whether a chemical is present in a test specimen or not, preferably,

the kit, wherein cell response to a chemical is life or death of a cell, and/or a change in the proliferating ability, aspiration amount, enzyme activity and/or gene expression, further preferably,

the kit, wherein the change in gene expression is a change in a RNA amount or a mRNA amount, more preferably,

the kit, wherein the change in gene expression is measured by reporter gene assay,

Please replace the paragraph beginning at page 8, line 24 with the following rewritten version:

~~(5)~~ A fifth aspect of the present invention is the kit according to the ~~(4)~~fourth aspect, wherein the microorganism is yeast and the gene to be disrupted is defined in the (2), and the kit according to the (4), wherein the microorganism is a microorganism other than yeast, and the gene to be disrupted is a gene corresponding to a gene as defined in the (2),

Please replace the paragraph beginning at page 9, line 7 with the following rewritten version:

~~(6)~~ A sixth aspect of the present invention is a composition for examining whether a chemical is present in a test specimen or not, comprising a gene-disrupted strain of a microorganism, preferably,
the composition, wherein cell response to a chemical is life or death of a cell, and/or a change in the proliferating ability, an aspiration amount, enzyme activity and /or gene expression, further preferably,
the composition, wherein the change in gene expression is a change in a RNA amount or a mRNA amount, more preferably, the composition, wherein the change in gene expression is measured by reporter gene assay,

Please replace the paragraph beginning at page 9, line 18 with the following rewritten version:

~~(7)~~ A seventh aspect of the present invention is the composition according to the ~~(6)~~ the sixth aspect, wherein the microorganism is a microorganism other than yeast, and the gene to be disrupted is defined in the ~~(2)~~ second aspect, and the composition according to the ~~(6)~~ sixth aspect, wherein the microorganism is a microorganism other than yeast, and the gene to be disrupted is a gene corresponding to a gene as defined in the ~~(2)~~ second aspect, and

Please replace the paragraph beginning at page 9, line 25 with the following rewritten version:

~~(8)~~ An eighth aspect of the present invention is a use of a gene-disrupted strain of a microorganism for examining whether a chemical is present in a test specimen or not, preferably,
the use, wherein cell response to a chemical is life or death of cell a and/or a change in the proliferating ability, an aspiration amount, enzyme activity and/or gene expression, further preferably,
the use, wherein the change in gene expression is a change in a RNA amount or a mRNA amount, more preferably,
the use, wherein the change in gene expression is measured by reporter gene assay,

Please replace the paragraph beginning at page 10, line 11 with the following rewritten version:

(9) A ninth aspect of the present invention is the use according to the (8) eighth aspect, wherein the microorganism is a microorganism other than yeast, and the gene to be disrupted is defined in (2) the second aspect, and the use according to the (8) eighth aspect, wherein the microorganism is a microorganism other than yeast, and the gene to be disrupted is a gene corresponding to a gene as defined in the (2) second aspect.

Please replace the heading at page 13, line 21, with the following rewritten version:

~~Best mode for carrying out the invention~~ DETAILED DESCRIPTION OF THE
INVENTION

Please add the following new heading at page 64, between lines 1 and 2:

WHAT IS CLAIMED IS: